Synthesis of 18-Demethyltaxoid *via* Stereoselective Allylation and Intramolecular Aldol Condensation Reactions

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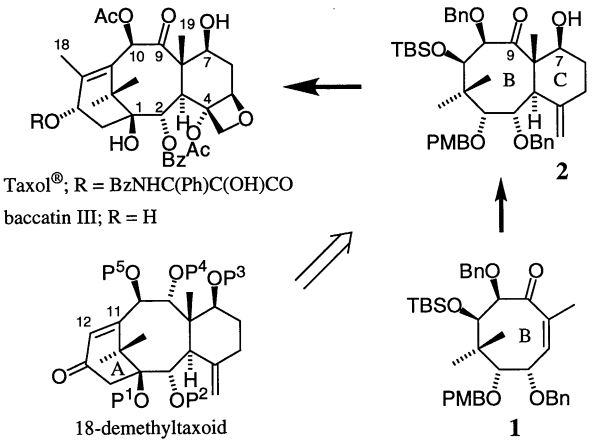
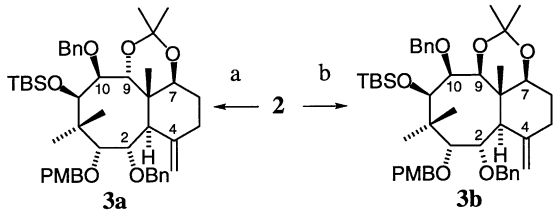
Optically active novel 18-demethyltaxiods were successfully synthesized from 2α,10β-dibenzyloxy-11β-(*t*-butyldimethylsiloxy)-7β-hydroxy-1α-(*p*-methoxybenzyloxy)-8β,15,15-trimethyl-4-methylene-*trans*-bicyclo[6.4.0]dodecan-9-one (**2**) which corresponds to the BC ring system of Taxol by stereoselective allylation and intramolecular aldol condensation reactions.

In the previous paper, it was reported that the asymmetric total synthesis of Taxol was completed by dehydration condensation between 7-TES baccatin III and protected *N*-benzoylphenylisoserines.[1] In the above synthetic strategy, 7-TES baccatin III was constructed from optically active polyoxy 8-membered ring compound **1** which corresponds to the B ring of Taxol. This route would possibly be applied to the asymmetric syntheses of other novel taxane derivatives such as 18-demethyltaxoids and 19-demethyltaxoids of which the basic carbon frameworks are partially modified and are hardly derived from naturally occurring taxoids.



Scheme 1.

In order to construct the A ring by cyclization and to form bridgehead double bond simultaneously onto the BC ring system, the strategy employing intramolecular aldol reaction between C11 and C12, and successive dehydration reaction was planned. In this strategy, it was assumed that the conformation of 8-membered ring would play a significant role in facilitating cyclization to give the A ring and formation of the bridgehead double bond. Conformational search using MMFF (Merck molecular force field) and semi empirical molecular orbital calculation with PM3 indicated that the most stable conformations of 8-membered rings in baccatin III and related taxoids are chair-boat forms as shown in Figure 1.[2] It was also informed by conformational studies on C7β,C9α-1,3-*trans*-acetonide **3a**, derived from the BC ring system **2** by reduction with DIBAL in CH_2Cl_2 and successive treatment with 2,2-dimethoxypropane and a catalytic amount of camphorsulfonic acid, that the conformation of 8-membered ring in this compound would be chair-boat form, while the conformation of 8-membered ring in C7β,C9β-1,3-*cis*-acetonide **3b**[1] was chair-chair form. Since the structure of carbon skeleton (from C2 to C10) in the BC ring system of **3a** is similar to that of baccatin III, it was expected that A ring closure reaction and formation of the bridgehead double bond would successively proceed by using a precursor which contains C7β,C9α-1,3-*trans*-diol unit in its BC ring system.



Scheme 2. Reagents and conditions: a) DIBAL, CH_2Cl_2, 0 °C to rt (83%); $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (quant.); b) AlH_3, toluene, -78 °C (94%); $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (quant.).

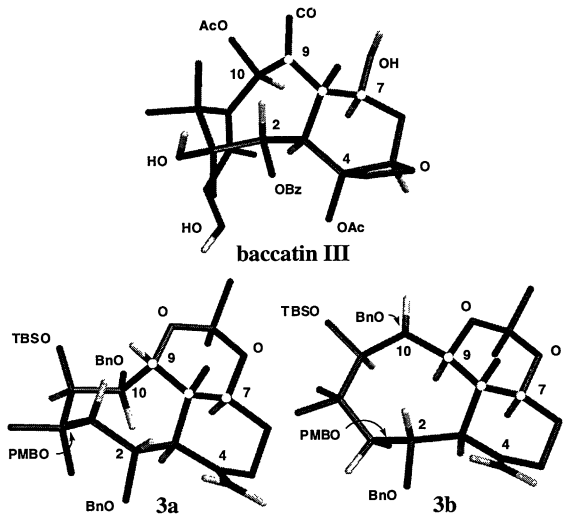
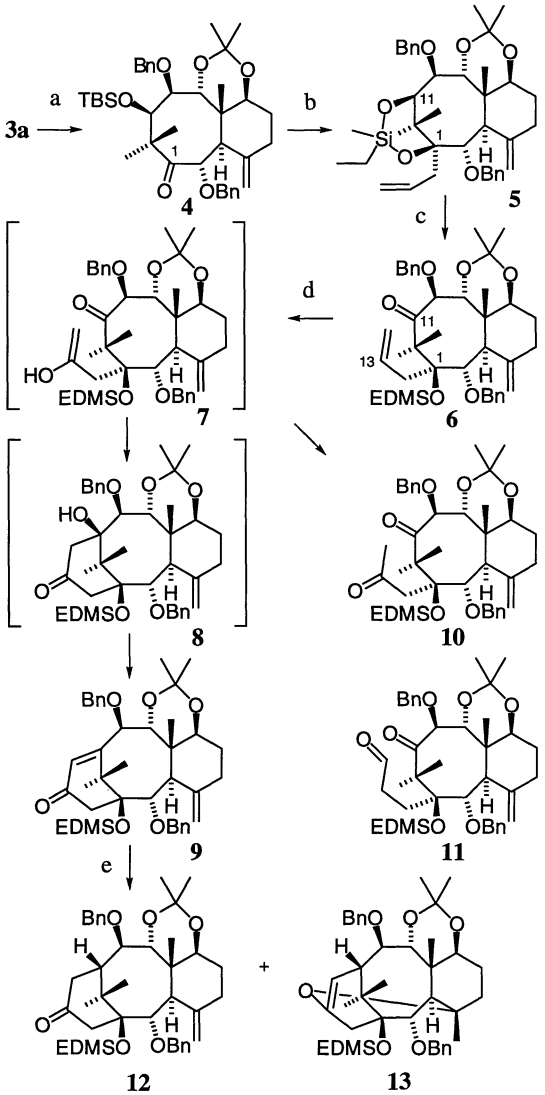


Figure 1. Stable conformations of baccatin III, acetonides **3a** and **3b** generated by calculation. Some atoms have been omitted for clarity.

Based on the consideration, the above C7β,C9α-1,3-*trans*-acetonide **3a** was converted to the corresponding 8-membered ring ketone **4** in good yield by oxidative cleavage of *p*-methoxybenzyloxy group with DDQ in the presence of H_2O and by following PDC oxidation of thus resulted secondary hydroxyl group at C1 position. Successive diastereoselective allylation in THF was carried out by using allylmagnesium bromide (1.0 M in Et_2O) to afford the desired homoallylic β-alcohol. 1,3-*Cis*-diol,

generated by desilylation of TBS group, was treated with ethylmethylsilyl bis(trifluoromethanesulfonate) in pyridine to yield silylene compound **5**, which was then transformed to the trialkylsilylether (ethyldimethylsiloxy group = EDMSO) at the C1 position by way of alkylation of bridged silicon atom with MeLi in toluene at low temperature.[3] Thus formed secondary hydroxyl group at C11 position was oxidized with PDC to afford ketone **6** in good yield. On the other hand, when this alkylation of **5** was tried in Et_2O or THF, undesirable trialkylsilylether at the C11 position was formed as a major product.

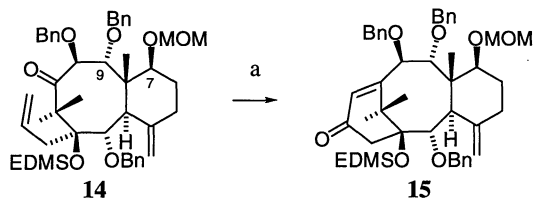
Subsequently, synthesis of diketone **10** corresponding to the precursor of ABC ring system was tried by using Wacker oxygenation at C13 position of ketone **6**. Then, it was found out that 18-demethyltaxoid **9**, the targeted molecule of the present approach, was obtained in 60% yield as a mixture of slowly interconverting conformational isomers along with a mixture of diketone **10** and ketoaldehyde **11** in 8% yield (**10** : **11** = ca. 3 : 5) under forced Wacker reaction conditions at 45 °C for 3 h. Precise structure of **9** was determined by ^1H NMR, IR and HR MS spectra of ketone **12** and enol ether **13** which were isolated after reduction of **9** with $NaBH_4$.



Scheme 3. Reagents and conditions: a) DDQ, H_2O, CH_2Cl_2, rt (92%); PDC, CH_2Cl_2, rt (92%); b) allyl-MgBr, Et_2O, -45 °C (quant.); TBAF, THF, 0 °C (quant.); $EtMeSi(OTf)_2$, Py, 0 °C (quant.); c) MeLi, toluene, -45 °C (83%); PDC, CH_2Cl_2, rt (86%); d) $PdCl_2$, DMF, H_2O, 45 °C (60% of **9** and 8% of a mixture of diketone **10** and ketoaldehyde **11**); e) $NaBH_4$, MeOH, 0 °C (24% of **12** and 71% of **13**).

The reaction is assumed to proceed by the following mechanism; in the first place, enol **7** is temporally generated *via* successive hydration of vinyl palladium(II) complex and β-elimination of palladium(0) from thus formed intermediate. Secondly, successive intramolecular aldol reaction takes place to give the desired aldol **8**, since the Wacker oxygenation is carried out under relatively acidic conditions. Thus formed aldol **8** is unstable compared to α,β-unsaturated ketone **9** because of the conformational effect of BC ring system so that subsequent dehydration reaction of **8** proceeds smoothly to afford 18-demethyltaxoid **9** which includes bridgehead double bond.

According to almost the same procedures, a derivative of ketone **6** possessing different acyclic protecting groups at C7 and C9 positions was prepared from the C7β,C9α-1,3-*trans*-diol. Wacker oxygenation was also performed on treating this ketone **14** with $PdCl_2$ under the conditions similar to the case of ketone **6** to produce a 18-demethyltaxoid **15**, as expected.



Scheme 4. Reagents and conditions: a) $PdCl_2$, DMF, H_2O, 45 °C (51% of **15** and 7% of a mixture of the corresponding diketone and ketoaldehyde (ca. 2 : 5).

As described above, the stereoselective syntheses of 18-demethyltaxoids were accomplished *via* diastereoselective allylation of bicyclic 8-membered ring ketones, which possess C7β,C9α-1,3-*trans*-diol units, derived from aldol **2** corresponding to the BC ring system of Taxol, and successive forced Wacker oxygenation and intramolecular aldol reactions in one-pot.

Thus, it is noted that our previously reported synthetic strategy for the synthesis of Taxol is further applied to syntheses of other taxane derivatives, which are hardly derived from naturally occurring taxoids such as 10-deacetylbaccatin III.

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References and Notes

1 T. Mukaiyama, I. Shiina, H. Iwadare, M. Saitoh, T. Nishimura, N. Ohkawa, H. Sakoh, K. Nishimura, Y. Tani, M. Hasegawa, K. Yamada, and K. Saitoh, *Chem. Eur. J.*, **5**, 121 (1999), and references cited therein.

2 Conformational search was performed with the program package SPARTAN 5.0.3 (DEC version) of Wavefunction, Inc.

3 T. Mukaiyama, I. Shiina, K. Kimura, Y. Akiyama, and H. Iwadare, *Chem. Lett.*, **1995**, 229.